II. REMARKS

A. Status of the Claims

Claims 1, 2, 5, 14-17, 23-28, 31-51, and 60 were pending in the case at the time of the Office Action, with claims 5, 14-17, 23-28, and 34 having been previously withdrawn from consideration as being directed to a non-elected invention. Claims 2, 31, 32, 35, and 42 have been amended in the Amendment set forth herein. New claim 61 has been added. Claims 1, 3-4, 6-13, 18-22, 29-30, and 52-59 have been canceled without prejudice or disclaimer. Therefore, claims 2, 31-33, 35-51, and 60-61 are currently under consideration.

B. The Double Patenting Rejections Are Overcome

Claims 1, 2, and 31-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of U.S. Patent 6,692,724. Claims 35-41 are rejected on the ground of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent 7,067,111. In the interest of advancing prosecution and without conceding that the claims are unpatentable over the cited patents, Applicants will file terminal disclaimers to overcome these rejections.

Claim 38 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 52-73 of copending application No. 10/672,763. Claims 42-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-50 and 74-81 of copending application 11/405,334. Applicants understand that these rejections are only provisional. Applicants will address these rejections once they are no longer provisional.

C. The Claim Rejections Under 35 U.S.C. §102 Are Overcome

1. Rejections Based on Srinivasan Are Overcome

Claims 1, 32, 33, 38, and 39 are rejected under 35 U.S.C. §102(b) as being anticipated by Srinivasan (U.S. Patent 5,310,536). Applicants respectfully traverse.

Without conceding that the claims as originally written would have been anticipated by Srinivasan, Applicants note that claim 1 has been canceled without prejudice or disclaimer. Further, it is noted that claim 32 has been amended to depend from claim 2 (a claim not included in this rejection and thus not considered unpatentable over Srinivasan) rather than claim 1. Thus, the rejection of claim 32 is moot. Further, the rejection of claim 33 is moot because it depends from claim 32 and thus includes the limitations of claim 32. Claim 38 recites that the compounds include the limitations of amended claim 32, and claim 39 depends from claim 38. New claim 61 depends from claim 60, a claim not included in this rejection and thus considered nonobvious by the Examiner. In view of the foregoing, the rejection of the claims under 35 U.S.C. §102 based on Srinivasan is moot.

2. Rejections Based on Klaveness Are Overcome

Claims 1, 32, 33, 38, 39, and 41 are rejected under 35 U.S.C. §102(b) as being anticipated by Klaveness *et al.* (WO 98/047541; hereinafter "Klaveness"; whereby U.S. 6,610,269 is relied upon as equivalent). Applicants respectfully traverse.

Without conceding that the claims as originally written would have been anticipated by Klaveness, Applicants note that claim 1 has been canceled without prejudice or disclaimer. Further, it is noted that claim 32 has been amended to depend from claim 2 (a claim not included in this rejection and thus not considered unpatentable over Klaveness) rather than claim 1. Further, it is noted that claim 32 has been amended to depend from claim 2 (a claim not included

in this rejection and thus not considered unpatentable over Klaveness) rather than claim 1. Thus, the rejection of claim 32 is moot. Further, the rejection of claim 33 is moot because it depends from claim 32 and thus includes the limitations of claim 32. Claim 38 recites that the compounds include the limitations of claim 32, and claim 39 depends from claim 38. New claim 61 depends from claim 60, a claim not included in this rejection and thus considered nonobvious by the Examiner. In view of the foregoing, the rejection of the claims under 35 U.S.C. §102 based on Klaveness is moot.

D. The Claim Rejections Under 35 U.S.C. §103 Are Overcome

1. The Rejections Based on Iyer in View of Zareneyrizi

Claims 1, 2, 31-33, 35-48, 51, and 60 are rejected under 35 U.S.C. §103(a) as being unpatentable over Iyer *et al.* (J. Nucl. Med., 2001, 42, p. 96-105; hereinafter "Iyer") in view of Zareneyrizi *et al.* (Anti-Cancer Drugs, 1999, 10. p. 685-692; hereinafter "Zareneyrizi"). Iyer concerns ^{18}F-labeled penciclovir as a probe for imaging HSV1-thymidine kinase reporter gene expression. Zareneyrizi discloses synthesis of ^{99m}Tc-ethylenedicysteine (EC) colchicine to assess tumor microvasculature density. The Examiner argues that one of ordinary skill in the art would be motivated to substitute the ^{18}F label of the penciclovir of Iyer with ^{99m}Tc-EC of Zarencyrizi to lead to ^{99m} Tc-EC-penciclovir. Applicants respectfully traverse.

In rejecting claims under 35 U.S.C. §103(a), the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent

decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that in setting forth a *prima facie* case of obviousness, it is necessary to show "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 127 S.Ct. 1727 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The Examiner has failed to establish a *prima facie* case of obviousness because the Examiner has not set forth sufficient reason with rational underpinning as required by *KSR* to support a *prima facie* case of obviousness. Iyer teaches ^{18}F labeling of penciclovir. There is no rational basis as to why one of ordinary skill in the art would be motivated to replace the ^{18}F of Iyer with ^{99m}Tc-EC of Zareneyrizi. Nothing in Iyer teaches or suggests substituting ^{18}F with a chemical moiety, such as a radiolabeled N_2S_2 chelate, for imaging. Rather, Iyer appears to focus solely on probes with single atom radiolabels, including ^{18}I, ^{124}I, ^{3}H labeled chemical substrates. In fact, Iyer suggests that substitution with a chemical moiety would not result in an effective reporter, which actually seems to teach away from the claimed invention. For example, on page 97, second full paragraph, Iyer teaches that slight structural variations have a significant effect on biological activity. In particular, Iyer teaches that "the lack of an ether oxygen in the side chain of PCV has a significant effect on its biological properties," even though PCV is "structurally similar to GCV." Page 97, second paragraph. Thus, Iyer actually teaches away from substituting the single atom radiolabel (e.g., 18F) with a substantially larger moiety such as 99mTc-EC.

Furthermore, one of ordinary skill in the art would not be motivated to substitute the colchicine moiety of Zareneyrizi's ^{99m}TC-colchicine conjugate with penciclovir. Iyer teaches that PCV is useful for imaging of "HSV-tk gene expression *in vivo*." Abstract. Iyer also teaches

that "PCV is a highly selected antiherpes virus agent" and that "after transport into cells, PCV gets phosphorylated by HSV1-TK to the monophosphate, which subsequently undergoes further phosphorylation by cellular kinases to its corresponding di- and triphosphates" with the triphosphates becoming incorporated into DNA to inhibit viral synthesis. Page 97, second full paragraph. Iyer further teaches that while "PCV is phosphorylated efficiently in herpes virus-infected cells, the mammalian thymidine kinases phosphorylate phosphorylates PCV only minimally." *Id.* One of ordinary skill in the art would not be motivated to substitute the colchicine of Zareneyrizi with penciclovir because Iyer does not teach that PCV is effective for imaging of cells that do not express HSV-tk. There is no information in Zareneyrizi to suggest that the mammalian cells/tumors that were evaluated therein were transfected with herpes virus. Thus, if anything, Iyer actually ***teaches away*** from imaging the cells of Zareneyrizi using ^{99m}Tc-EC-penciclovir.

The Examiner argues that it was well-known in the diagnostic arts to substitute one reporter probe, or targeting moiety, for another. The Examiner has not cited any evidence to support this assertion. As discussed above, Iyer teaches that slight structural variations have a significant effect on biological activity. This teaching in Iyer actually counters the Examiner's assertion. Further, Iyer teaches superiority of penciclovir over ganciclovir in reporting HSV-tk expression in cells, thus clearly teaching that moieties, whether for reporting or targeting, are indeed not so interchangeable.

In view of the foregoing, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. No reasonable basis with rational underpinnings has been set forth for why one of ordinary skill in the art, in view of the teachings of these references, would combine the reference teachings to lead to the claimed invention because these

references actually teach away from the claimed invention. Further, new claim 61, which depends from claim 60, would also be nonobvious for the foregoing reasons. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) based on Iyer in view of Zareneyrizi.

2. The Rejections Based on Iyer in View of Zareneyrizi and Further in View of Belinka

Claims 1, 2, 31-33, 35-51, and 60 are rejected under 35 U.S.C. §103(a) as being unpatentable over Iyer (as above) in view of Zareneyrizi (as above) and further in view of Belinka (U.S. Patent 5,609,847; hereinafter "Belinka"). The teachings of Iyer and Zareneyrizi are as discussed above. The Examiner adds in Belinka to provide a teaching that kits may include gluconate or glucarate as transition chelators. The Examiner proceeds to argue that "it would have been obvious to one in the art to substitute gluconate or glucarate for EDTA as a functionally equivalent chelator in the kid of Zareneyrizi." Office Action, page 10. Applicants respectfully traverse.

Applicants note that the Examiner appears to have misunderstood the claims. The claims do not concern the substitution of one chelator for another. The Examiner is directed, for example, to the claim 48, which recites a kit ... "further comprising a transition chelator" and claim 48 reciting specific examples of transition chelators, including gluconate and glucarate. The "further comprising" language means that the kit, which already includes an N_2S_2 chelate-targeting ligand conjugate in accordance with claim 2 and a reducing agent, further includes a transition chelator (and not replacement of one chelator for another). Gluconate and glucarate moieties do not fall within the scope of the formula as chelator moieties in claim 2.

For the reasons set forth in the foregoing section, Iyer in view of Zareneyrizi fails to disclose the N_2S_2 chelate-targeting ligand conjugates as set forth in claim 2. Belinka fails to remedy the deficiencies of these references because it is only cited as teaching kits that include glucarate and gluconate, two transition chelators, and interchangeability of certain chelators. Without concurring with the Examiner regarding the teachings of Belinka, Applicants note that Belinka fails to provide the missing motivation to provide for the chelator-targeting ligand conjugates as set forth in claim 2. Thus, Belinka fails to remedy the deficiencies of Iyer and Zareneyrizi.

In view of the foregoing, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. No reasonable basis with rational underpinnings has been set forth for why one of ordinary skill in the art, in view of the teachings of these references, would combine the reference teachings to lead to the claimed invention. Further, new claim 61, which depends from claim 60, would also be nonobvious for the foregoing reasons. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) based on Iyer in view of Zareneyrizi and further in view of Belinka.

E. The Claim Objections Are Overcome

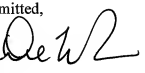
Claims 1, 2, 31-33, 35-51 and 60 are objected to for reciting certain species twice, including herceptin, angiostatin, and thalidomide. Applicants have amended the claims to omit duplicative language. Therefore, the objections are overcome.

F. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is

invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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